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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/872,364

Applicant(s)

THASTRUP ET AL.

Examiner

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☐ Claim(s) 1-12, 14, 18, 20, 21, 23, 26, 37-46 and 48-50 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-3, 8-12, 18, 20, 21, 23, 26, 37-46, 48, 49 is/are rejected.
- 7) ☐ Claim(s) 4-7, 14 and 50 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |  |
|---|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)            |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____  |

### DETAILED ACTION

1. Claims 14, 18 and 23 have been amended. Claims 28-32, 35, 37 and 47 have been canceled. Claims 48-50 have been added. Claims 1-12, 14, 18, 20, 21, 23, 26, 37-46 and 48-50 are under consideration.

2. Claims 18, 20, 21, 23, 26 and 38-46, 48 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite the limitations of Green Fluorescent Protein. The metes and bound of what constitutes a "green fluorescent" protein cannot be determined as it is unclear whether the recitation of "green fluorescent protein" is intended to limit the protein to that isolated from *A. victoria*, or if other green fluorescent proteins, such as those isolated from other organisms producing fluorescent proteins such as the coral, as included within this definition. Also it is unclear if "green" is intended to limit the emission spectrum to a specific range of wavelengths, or if variants of the green fluorescent protein as isolated from *A. victoria*, which exhibit a differing emission spectrum, such as the red-shifted variant, are included within the definition of a green fluorescent protein. Further, it is unclear if the terms encompass proteins having a green fluorescence emission spectrum, wherein said proteins are not obtained from a fluorescent jellyfish, such as proteins which are produced by site-directed mutagenesis in a laboratory. The specification states on page 7, lines 11-24 that a preferred embodiment of the invention is the green fluorescent protein derived from *A. victoria*. However, this does not constitute a limiting definition for green fluorescent protein. Further, the specification states on page 7, lines 23-24 that novel fluorescent proteins may be derived from *R. reniformis*. Thus, the specification is contemplating fluorescent proteins which are not limited to those found in *A. victoria*. Accordingly, for purpose of examination, all alternatives of fluorescent protein will be considered without regard to origin or color of emission spectra.

Applicant argues that allelic differences exist between genes encoding the green fluorescent proteins obtained from jelly fish, and that the color "green" is not limited to fluorescent proteins which are green because other fluorescent proteins of red, yellow and blue can be found within jellyfish. Applicant argues that those of skill in the art are fully able to

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ascertain the metes and bounds of the term "green fluorescent protein". this has been considered but not found persuasive. The instant claims are not limited to green fluorescent proteins isolated from jellyfish, nor are they limited to fluorescent proteins of the color green. Thus, the metes and bounds of "green fluorescent protein" are unclear.

3. Claims 26, 48 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 26 further limits claim 18. Claim 26 recites "at least a Leu residue substituted for the Phe residues at position 64 of SEQ ID NO:22". Claim 18 recites "an amino acid sequence selected from the group consisting of "Leu, Ile, Val, Gly and Ala". Claim 26 is broader in scope than claim 18 because it allows for more than the substitution of "Leu, Ile, Val, Gly and Ala" by the recitation of "at least".

The metes and bounds of the claims 48 and 49 cannot be determined as it is unclear if the GFP is intended to be the substituted GFP or the GFP from which the variant protein is made.

4. The rejection of claims 18, 20, 21, 23, 26, 38-46, 48 and 49 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record.

The instant claims are drawn to the nucleic acids encoding fluorescent proteins which minimally comprise a fluorescent chromophore of SerTyrGly, SerHisGly, ThrHisGly or ThrTyrGly, immediately followed by Leu, Ile, Val, Gly, or Ala. The claims encompass a genus of nucleic acid which are reliant upon the identity of fluorescent proteins of any color and from any organisms which minimally comprise four consecutive amino acids. The specification sets forth SEQ ID NO:16, 18, 20 and 22 as fluorescent proteins of the instant invention. For the reasons set forth in the rejection under 112, second above, the metes and bounds of the instant claims cannot be determined as the structure and function of the proteins encoded thereby are not limited. The specification teaches variants of SEQ ID NO:22, wherein amino acid residue 64 is

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either Leu, Ile, Val, Gly, or Ala and wherein residues 65-67 are SerTyrGly, SerHisGly, ThrHisGly or ThrTyrGly. The disclosed variants of SEQ ID NO:22 (SEQ ID NO:16, 18 and 20) fail to anticipate the claimed genus of proteins because the genus encompasses proteins having an unlimited number of structural alterations, in addition to those disclosed, in addition to having an emission spectrum which is not confined to a range of wavelengths which would be green. Thus, the genus of proteins is variant, encompassing numerous structural and functional modifications, as evidenced from the art rejections below. One of skill in the art would conclude that applicant did not disclose a representative number of species to describe the genus of proteins on which the genus of nucleic acids depends.

Applicant argues that the genus is not highly variant because claim 18 has been amended to recite only one substitution before the specific chromophore as recited. This has been considered but not found persuasive. Even with the limitation that a single amino acid is substituted, rather than "at least" an amino acid, the genus of proteins is highly variant with respect to the remainder of the amino acid sequence, beyond that of the four consecutive amino acids specified by the claim. The genus of protein relied upon in amendment claim 18 need only minimally comprise four consecutive amino acids, and the stating fluorescent protein may be derived from any organism and have any color. It is noted that the fluorescent proteins of *A. victoria* are about 230 amino acids in length. In contrast the instant claims specify a genus of proteins having only a required four contiguous amino acids. thus, the examiner maintains that the decryption of SEQ ID NO:16, 18, 20 and 22 does not adequately describe the protein genus because the genus encompasses proteins which differ significantly in structure from SEQ ID NO:16, 18, 20 and 22.

Applicant argues that the enhancing effect applies both to the blue GFP (Y66H-GFP) and to the red-shifted variant (S65T-GFP). This has been considered but not found persuasive. this is a rejection based on lack of written description, not on lack of enablement. further, the instant claims are not limited to the nucleic acid encoding Y66H-GFP or S65T-GFP.

5. Claims 18, 20, 21, 23, 26, 39, 40, 43-46 and 48 are rejected under 35 U.S.C. 102(a) as being anticipated by Ward et al (WO 95/21191).

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Claim 18 is drawn to a nucleotide sequence encoding a green fluorescent protein having an amino acid sequence in which the amino acid Phe immediately upstream of the chromophore is substituted with an amino acid selected from the group consisting of Leu, Ile, Val, Gly, and Ala, wherein said chromophore has an amino acid sequence selected from the group consisting of SerTyrGly, SerHisGly, ThrHisGly and ThrTyrGly, and wherein said substituted GFP exhibits increased fluorescence at the same wavelength at a temperature of 30 degrees or above, relative to a GFP lacking the above substitution, when expressed in a host cell. Claim 20 is drawn to an expression vector comprising suitable expression control sequences operatively linked to a nucleic acid molecule of claim 18. Claim 21 is drawn to a recombinant cell comprising an expression vector that comprises a suitable expression control sequence operatively linked to the nucleic acid molecule of claim 18. Claim 23 is drawn to a nucleic acid molecule comprising a nucleotide sequence encoding a protein of interest fused to a nucleotide sequence encoding a green fluorescent protein according to claim 18. Claim 26 is included in this rejection as the metes and bounds of the claim with regard to SEQ ID NO:22 are unclear. Claim 39 embodies the nucleic acid of claim 18 wherein a Ile residue is substituted for a Phe residue. Claim 40 embodies the nucleic acid of claim 18 wherein a Ala residue is substituted for a Phe residue. Claim 43-45 embody the nucleic acid molecule of claim 18 wherein said substituted GFP exhibits increased fluorescence at the same wavelength and at a temperature of from 32 degrees to 39 degrees, from 35 degrees to 38 degrees and at a temperature of about 37 degrees, respectively. Claim 46 embodies the nucleic acid according to claim 18 wherein said GFP is A victoria GFP or R reniformis GFP. Claim 48 embodies the nucleic acid of claim 18 wherein said GFP is obtained from Aequoria victoria. Claim 46 embodies the nucleic acid of claim 18 wherein the GFP is derived from A. victoria or R. reniformis.

Ward et al disclose the nucleic acid sequence of SEQ ID NO:2) encoding a modified A victoria GFP (SEQ ID NO: 1), wherein said modified sequence comprises ThrTyrGly (residues 38-40 of SEQ ID NO:1), which is followed immediately upstream by a Ala (residue 37) or and ThrHisGly (residues 230--232 of SEQ ID NO:1) which is followed immediately upstream by a Ile (residue 229). Ward et al disclose expression vectors comprising said sequence wherein said vector is fused to a protein of interest, wherein said protein of interest confers drug resistance, such as ampicillin (page 12, lines 7-11), or wherein said protein of interest is a luciferase (page

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12, lines 18-27). Ward et al do not identify residues 37-40 or 230-232 as a chromophore, or compare the level of fluorescence to a protein having a Ile or Ala at residues 37 or 229, respectively with the corresponding protein having at Phe at position 37 or 229, however, the properties of having the claimed chromophore preceded by a Ala or Ile residue are the same as that claimed. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

6. The provisional rejection of claims 1-3, 8, 9, 10, 11, 12, 18, 20, 21, 26 and 38-46 under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 10-15, 28-31 and 33 of copending Application No. 09/619,310 is maintained for reasons of record. Claims 48-50 are also rejected for the same reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the '310 application anticipate the instant claims drawn to SEQ ID NO:16, 18 and 20 as well as instant claims 18 and 35 drawn to a nucleic acid molecule comprising a nucleotide sequence encoding a green fluorescent protein having the which has been modified by an amino acid substitution of Leu, Ile, Val, Gly or Ala immediately upstream of the chromophore.

This is a provisional obviousness type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant argues that the M.P.E.P. 804) requires the examiner to withdrawn a provisional-type double patenting rejection if it is the only rejection remaining, and therefore enabling the issue of said application. This argument is moot because the instant application is still rejected under 112, first and second paragraphs and 102(e).

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7. Claims 4-7, 14, 50 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. All other rejections and objections as set forth in the previous Office action are withdrawn.


*Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

Karen A. Canella, Ph.D.

Primary Examiner, Group 1642

02/18/04

  
**KAREN A. CANELLA PH.D**  
**PRIMARY EXAMINER**